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SEX-SPECIFIC MORTALITY FROM ADULT T-CELL LEUKEMIA AMONG CARRIERS OF HUMAN T-LYMPHOTROPIC VIRUS TYPE I

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Perinatal infection with human T-lymphotropic virus type I (HTLV-I) is considered a risk factor for adult T-cell leukemia (ATL). Incidence of ATL in Japan is generally higher in males compared with females, perhaps partly due to an earlier average age of infection among males. We estimated sex-specific ATL mortality among perinatally-infected HTLV-I carriers in the prospective Miyazaki Cohort Study in Japan. Based on the approximated proportion of perinatally-infected carriers, the relative risk (RR) of ATL for males compared with females was calculated. Six ATL deaths (4 males, 2 females) occurred among the 550 HTLV-I carriers in the cohort during 13 years of follow-up. The overall ATL mortality was 190.5 (95% CI 51.9–487.7) per 10^5 person-years for males and 51.7 (6.3–186.8) per 10^5 person-years for females (age-standardized RR = 3.9, p=0.02). By approximating the number of persons who acquired infection perinatally, the estimated mortality among those perinatally-infected HTLV-I carriers was 209.1 (57.0–535.2) per 10^5 person-years for males and 60.9 (7.4–219.9) per 10^5 person-years for females (age-standardized RR = 3.7, p=0.02). The adjusted RR changed minimally from the unadjusted RR, suggesting that earlier age of infection alone is unlikely the explanation for the male predominance in ATL. Based on the small number of cases available for analysis, aspects of gender itself appear to play a role in the development of this malignancy.

Key words: *ATL; mortality rate; sex-specific; perinatal infection; HTLV-I*

Adult T-cell leukemia (ATL) is a malignancy of activated CD4+/CD25+ T-lymphocytes, caused by human T-lymphotropic virus type I (HTLV-I) infection.[1,2] It develops many decades after initial HTLV-I infection,[3,4] with an estimated lifetime risk of less than 5% among HTLV-I carriers.[5] The reported incidence of ATL in Japan is higher in males than in females.[5–8] In the population-based Miyazaki Cohort Study in southern Japan, we have found that correlates of risk for ATL among HTLV-I carriers, including proviral load, levels of detectable mRNA for tax regulatory proteins and presence of circulating abnormal lymphocytes, are also higher in males than in females.[9–11]

Perinatal infection appears to be a strong risk factor for ATL,[12] whereas those who have acquired infection later in life do not appear to be at risk for this malignancy. Since sexual transmission of the virus occurs predominantly from male to female,[13,14] a larger number of females than males becomes infected with HTLV-I in adult life. Thus, direct calculation of ATL incidence or mortality rates would include a larger proportion of person-years of observation for females who were not infected perinatally and consequently not at risk for ATL. This would underestimate the risk of ATL among females HTLV-I carriers, with an overestimation of the male-to-female ratio with regard to disease occurrence. However, because age of infection is rarely identifiable for individual carriers, the risk of ATL, as well as the difference in risk by gender, among perinatally-infected HTLV-I carriers are generally difficult to assess.

In the present study, we estimated the proportion of HTLV-I carriers who acquired infection prior to adolescence, using the observed HTLV-I seroconversion rate within a well-defined study population. Based on these estimates, we calculated the sex-specific mortality rate and the male-to-female ratio of ATL among perinatally-infected HTLV-I carriers.

MATERIAL AND METHODS

Study subjects

The prospective Miyazaki Cohort Study was established in 1984 in 2 HTLV-I endemic villages in Miyazaki Prefecture, Japan.[15] Approximately 27% of 2,005 cohort members enrolled as of November 1997 were HTLV-I seropositive at baseline. The cohort has been followed for clinical, serologic, demographic and behavioral data in the context of free health examinations offered annually by the government for those aged 40 years or older. For our study, younger villagers may also attend. Informed consent was obtained from all study participants. The study protocol was approved by the institutional review boards of the Harvard School of Public Health and the Miyazaki Medical College. Annual screens consist of a physical examination, other routine health examinations and blood tests. Public health nurses monitor the mortality and changes in residence among the population. Deaths from ATL are identified through monitoring and confirmed by medical records or reports from the local public health nurses. The present analysis includes a total of 550 HTLV-I carriers in the Miyazaki Cohort Study, including 24 subjects who seroconverted since the study enrollment and 526 prevalent HTLV-I positive subjects.

Statistical analysis

Total person-years of observation were calculated from the date of a subject's first health examination when s/he was HTLV-I positive to the date of death, loss to follow-up or last census of vital status (June 1997), whichever came first. The overall mortality rate was calculated as the observed number of ATL deaths divided by the total person-years of observation. Exact 95% confidence intervals (CIs) were obtained, assuming a Poisson distribution for the number of ATL deaths in the cohort. The relative risk (RR) of ATL mortality for males compared with females was calculated as the ratio of the age-standardized mortality rates, taking the age distribution of the entire cohort population as the standard. The p-value for the RR was calculated using the exact binomial distribution.

Although the age-related increase in the HTLV-I seroprevalence may in part be due to a cohort effect,[13] it is impossible to separate the magnitude of an effect related to perinatal transmission from one related to sexual transmission. In order to avoid inaccurate modeling assumptions with regard to a possible cohort effect, we employed the following approach: The proportion of subjects who had acquired HTLV-I infection perinatally was derived indirectly by using the observed seroconversion rates within the HTLV-I

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negatives in the study cohort, which were 2.0 and 6.0 per 1,000 person-years between the ages of 50 and 69 years for males and females, respectively, and zero among those aged 70 years or older. A pattern of parallel increase in sex-specific HTLV-I seroprevalence in this cohort[15] suggests that the seroconversion rates were similar for both sexes between the ages of 20 and 50 years. Thus, the rate of 2.0 per 1,000 person-years was assumed for both men and women in these age groups, in which no seroconversions were observed during study follow-up (Table I). Based on the cultural and social mores of this older Japanese population, postperinatal infection among those under age 20 years was thought to have been minimal. Using these seroconversion rates, we estimated the number of HTLV-I seroconversions occurring after age 20 years among the 526 prevalent HTLV-I carriers prior to their entering the cohort study (Table I). The proportion of perinatally-infected HTLV-I carriers was then derived for each gender by the difference between the number of prevalent HTLV-I carriers and the expected number of seroconversions, divided by the number of prevalent HTLV-I carriers (91% for males, 85% for females for all age groups taken together). The adjusted person-years attributable to perinatal infection was calculated by multiplying these proportions by the total person-years of observation among the prevalent carriers. The adjusted mortality rate, that is, the mortality rate among presumed perinatally-infected HTLV-I carriers, was the ratio of the number of ATL deaths and the adjusted person-years.

RESULTS

Four males (64–83 years old) and two females (69 and 77 years old) died from ATL during study follow-up through June 1997. Details of these cases are described elsewhere.[16] The total person-years of observation accumulated by the 550 HTLV-I carriers, including 24 persons who seroconverted during the follow-up, were 2,099.5 for males and 3,865.7 for females. The crude mortality rate of ATL was 190.5 (95% CI 51.9–487.7) per 10^5 person-years for males and 51.7 (6.3–186.8) per 10^5 person-years for females. The age-standardized RR was 3.9 for males relative to females ($p=0.02$) (Table II).

The adjusted ATL mortality rate, based on person-years of observation attributable to perinatal transmission (1,913.3 for males, 3,282.9 for females), was 209.1 (57.0–535.2) and 60.9 (7.4–219.9) per 10^5 person-years for males and females, respectively. Thus, the rates among those HTLV-I carriers who were assumed to be perinatally-infected are 10% higher for males and 18% higher for females, compared with the overall rate based on all HTLV-I carriers. The age-standardized RR among perinatally-infected HTLV-I carriers was 3.7 for males compared with females ($p=0.02$) (Table II).

TABLE I – PERSON-YEARS AT RISK FOR SEROCONVERSION PRIOR TO STUDY ENROLLMENT, ESTIMATED SEROCONVERSION RATES AND EXPECTED NUMBER OF SEROCONVERSIONS AMONG 526 PREVALENT HTLV-I CARRIERS IN THE MIYAZAKI COHORT STUDY BY SEX AND BY AGE CATEGORY

Age (years)	At risk person-years	Seroconversion rate (/1,000 person years)	Expected number of seroconversions since age 20[a]
Males			
20–29	1,908.6	2.0	3.8
30–39	1,871.0	2.0	3.7
40–49	1,717.8	2.0	3.4
50–59	1,248.0	2.0	2.5
60–69	633.8	2.0	1.3
70–79	245.9	0.0	0.0
80+	31.6	0.0	0.0
Σ (Males)	7,656.7		14.7
Females			
20–29	3,332.0	2.0	6.7
30–39	3,263.2	2.0	6.5
40–49	3,014.0	2.0	6.0
50–59	2,344.6	6.0	14.1
60–69	1,265.2	6.0	7.6
70–79	423.5	0.0	0.0
80+	42.0	0.0	0.0
Σ (Females)	13,684.5		40.9

[a]Estimated by multiplication of age-specific seroconversion rates and person-years at risk prior to study enrollment.

TABLE II – THE CRUDE AND AGE-STANDARDIZED RELATIVE RISK (RR) OF ADULT T-CELL LEUKEMIA MORTALITY AMONG ALL HTLV-I CARRIERS AND PERINATALLY-INFECTED HTLV-I CARRIERS IN THE MIYAZAKI COHORT STUDY

	MR (95% CI) [per 10^5 person-years]	Crude RR (p-value)	Age-standardized RR (p-value)
All HTLV-I carriers			
Males	190.5 (51.9–487.7)	3.7 (0.02)	3.9 (0.02)
Females	51.7 (6.3–186.8)	1.0	1.0
Perinatally-infected HTLV-I carriers			
Males	209.1 (57.0–535.2)	3.4 (0.03)	3.7 (0.02)
Females	60.9 (7.4–219.9)	1.0	1.0

MR, mortality rate; CI, confidence interval.

Because an underestimation of the seroconversion rate among younger females would have resulted in an overestimation of the gender ratio, we repeated the calculations using higher seroconversion rates. In a scenario where the HTLV-I seroconversion rate was assumed to be as high as 6.0 per 1,000 person-years among women throughout their reproductive years (age groups 20–29, 30–39 and 40–49 years), the estimated proportion of female HTLV-I carriers who acquired infection perinatally would have been 75%, yielding a male-to-female ratio of 3.0 ($p=0.03$).

Exclusion from the analysis of a male case whose ATL diagnosis antedated his enrollment into the study yielded a mortality rate of 142.9 (29.5–417.7) and 156.8 (32.4–458.4) per 10^5 person-years for males, without and with adjustment for perinatal infection, respectively. This exclusion resulted in a somewhat lower RR of 2.8 ($p=0.12$) for males compared with females, based on overall mortality rates, and 2.6 ($p=0.14$), based on mortality rates adjusted for perinatal infection.

DISCUSSION

The age of initial HTLV-I infection is postulated to be a crucial determinant of the risk of ATL.[7,17] If this hypothesis is true, the ATL risk among lifetime carriers of the virus may be higher than that among those who seroconverted later in life. In the present analysis, we calculated the rate of ATL death within a well-defined Japanese population with endemic levels of HTLV-I infection. We used the mortality rate in lieu of the incidence rate since the precise date of disease onset was unknown for some ATL cases. Because most of the ATL cases died within a year of diagnosis, the calculated mortality rate would likely approximate the incidence rate of the malignancy in this cohort. The overall mortality rates in the present study are comparable to the ATL incidence rates reported in other Japanese studies.[18,19]

We observed an overall 4-fold increase in the mortality from ATL for males relative to females. Other population-based studies and case series in Japan also have found a male predominance in ATL incidence but with lower RRs ranging from 1.7 to 2.6.[6,7] However, the reported gender ratio from the nationwide Japanese surveillance data for those aged 55 years or older appears to be higher than the ratio for those aged younger than 55 years old[18] and is comparable to the ratio estimated in the present study. Thus, the higher RR for males observed in our analysis is likely explained by the older average age of HTLV-I carriers in the Miyazaki cohort, in which limited data are available for those under age 40 years. Although an overestimation of the male-to-female ratio in the present study could have resulted from missed ATL diagnoses among those who were lost to follow-up, only 4% of all HTLV-I carriers were lost during the entire study period, which minimized the likelihood of substantial bias due to this mechanism. Moreover, there was no reason to expect that the loss to follow-up was differential by gender with regard to ATL de-

velopment, nor was there any reason to believe that there was sex-specific diagnosis bias.

A male predominance of ATL incidence has been a matter of debate because of the possibility of confounding by age of infection. In our analysis, the estimated ATL mortality rates adjusted for early life infection were 10% and 18% higher for men and women, respectively, than the overall sex-specific rates for all HTLV-I carriers. A significant increase in the male-to-female ratio even after adjustment for perinatal infection suggests that early infection alone does not entirely explain the gender difference in ATL incidence. In a recent article, Arisawa et al.[8] have reported a significant 2-fold increase in risk of ATL for males compared with females after accounting for differences in sex-specific HTLV-I seroprevalence. While adjustment of at-risk person-years may not have been exact in either study, these observations together support the contention that being male may be an independent risk factor for ATL in Japan.

The observed male predominance in ATL incidence is also consistent with our previous findings of a higher level of proviral load, mRNA for tax and circulating abnormal lymphocytes, three important correlates of HTLV-I pathogenesis, in males *vs.* females.[9–11] In contrast, Etoh et al.[20] found no gender difference in proviral load among HTLV-I-positive, Japanese blood donors. Selective enrollment of older subjects into our cohort study, as compared with relatively young subjects in the blood donor study, may have contributed to the discrepancy in the results. Evaluation of the association of HTLV-I proviral load with age would be useful in order to resolve this issue.

The present finding does contrast with a lack of gender effect on ATL incidence among HTLV-I carriers in Jamaica, after adjustment for age of infection.[21,22] While the Jamaican studies utilized historical population census data to estimate the HTLV-I seroprevalence and the amount of person-years attributable to early infection (younger than 20 years), our study estimated the person-years attributable to perinatal infection using the observed HTLV-I seroconversion rates from within the study cohort. Our calculations indicated that the proportion of female HTLV-I carriers who could have acquired infection in adulthood would not have exceeded 25%, yielding a 3-fold RR of ATL for males. The lack of an obvious male predominance in ATL incidence in Jamaica may be due, at least in part, to differences in host characteristics and other co-factors.

In conclusion, the results of the present analysis support a higher risk of ATL among older male HTLV-I carriers in Japan. A limitation of our study is the small number of cases, although to our knowledge this is one of the first to report sex-specific ATL mortality associated with perinatal infection in Japan. While some modeling assumptions may not be entirely correct, the use of observed seroconversion rates and careful sensitivity analysis provided us with a possible range for the mortality rate ratio. Our findings suggest that early life infection may explain only a part of the observed gender difference. Investigation of the host characteristics with respect to immune response to HTLV-I in the Japanese population in comparison with those in Jamaica may be useful in order to understand the biologic role of gender in the pathogenesis of HTLV-I.

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